Refine Search

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Terms	Documents
rotoevaporator adj15 (mm)	39

Database:
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DATE: Friday, January 19, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L4	rotoevaporator adj15 (mm)	39	L4
L3	rotoevaporator adj15 (300 adj1 mm)	0	L3
L2	rotoevaporator adj15 pressure	15	L2
L1	rotoevaporator adj10 pressure	15	L1

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Terms	Documents
L11 and (polyene or amphotericin)	8

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L12

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Search History

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L12	L11 and (polyene or amphotericin)	8	L12
L11	peg$pe adj5 micelle	27	L11
L10	peg$pe aj5 micelle	29769	L10
L9	l7 and amphotericin	29	L9
L8	(peg$ adj5 micelle) same peg$lipid	12	L8
L7	(peg$) adj5 micelle	157	L7
L6	(peg$$$asp)	12	L6
L5	(peg$asp) same peg$phospholipid	0	L5
L4	(peg$asp) same peg$dspe	0	L4
L3	(peg$asp) adj10 peg$dspe	0	L3
L2	(peg$asp)	12	L2
L1	(peg$asp) adj5 peg$dspe	0	L1

END OF SEARCH HISTORY

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L8: Entry 12 of 12 File: USPT Oct 6, 1998

DOCUMENT-IDENTIFIER: US 5817856 A
TITLE: Radiation-protective phospholipid and method

Detailed Description Text (27):
For use in cosmetic compositions, the PEG lipids may be formulated as liposomes, as micellar suspensions of varying consistencies, or in emulsions or microemulsions. The proportion of PEG lipid in the total lipid component may vary from 0.5 mol % to 100%, with the remainder preferably comprising vesicle-forming lipids, as discussed below. Formation of liposomes is most favorable at levels up to 25 mol % PEG-lipid. At levels of 25 mol % or greater of PEG-lipid, formation of micelles is favored.

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L8: Entry 11 of 12 File: USPT Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827533 A
** See image for Certificate of Correction **
TITLE: Liposomes containing active agents aggregated with lipid surfactants

Drawing Description Text (25):
FIG. 19 is a schematic of a PEG-lipid micelle, where the shaded region represents a PEG-rich layer around the micelle created by PEG grafted onto the lipids of the micelle.

Detailed Description Text (8):
In one series of experiments, the present inventors studied the influence of grafted PEG(750) as PEG-lipids on monooleoylphosphatidylcholine (MOPC) monomer exchange and micelle fusion with lipid bilayer vesicle membranes. The experimental results show that PEG(750)-lipid has a strong inhibitory effect such that micelle-membrane fusion decreases with increasing surface density of grafted PEG(750). At approximately 20 mol % PEG-lipid (corresponding to complete coverage of the membrane surface by PEG(750) "mushroom" structures as described below), micelle/membrane fusion is essentially prevented. The experimental data of the present inventors are well described by a model in which micelle-membrane fusion is considered a first order reaction process. The modeling of micelle-membrane fusion in the presence of grafted PEG(750), and the consideration of geometry characteristics of both PEG(750) "mushroom" and MOPC micelle, show that micelles must be in intimate contact with the headgroups of the membrane lipids in order for the fusion process to occur. Thermodynamic analysis and stationary equilibrium both suggest that the solution properties of surfactant in the aqueous and bilayer phases are not ideal, and that the surfactant molecules are slightly aggregated on average as trimers in the aqueous phase below the CMC. There may also be aggregation of surfactant molecules in the vesicle bilayer when exposed to surfactant concentrations above the CMC and this would be a first indication of defect formation that ultimately results in vesicle membrane breakdown and dissolution of the vesicle.

Detailed Description Text (9):
Thus the present inventors have found that polymers (such as polyethylene glycol (PEG)) grafted to lipids provide a strong steric repulsion against surface-surface and surface-macromolecule interactions. The present inventors studied the exchange of monooleoylphosphatidylcholine (MOPC) with vesicle membranes containing 750 dalton molecular weight surface-grafted PEG (incorporated as PEG-lipid) and have devised a simple energetic model for micelle uptake. In the experiments described herein, micropipet manipulation was used to support a single lipid vesicle and expose it to a flow of MOPC solution followed by a flow of MOPC-free bathing solution. MOPC uptake was detected by measuring increases in the projection length of the vesicle in the holding micropipet, which, at constant vesicle volume, is a direct measure of the vesicle area change (see FIGS. 1A and 1B; Examples 1 and 4). Control vesicles without grafted PEG showed saturable uptakes of approximately 5 mol % at MOPC concentrations of 3 micromolar (critical micelle concentration (CMC) of MOPC), while at 100 micromolar MOPC the control vesicles rapidly took up larger amounts (approximately 15 mol % of MOPC) and invariably broke up after only a few seconds. However, with increasing surface concentrations of PEG(750)-lipid in the vesicle membrane, the amount of MOPC taken up by the vesicle bilayer when exposed

to 100 .mu.M MOPC was reduced.

Detailed Description Text (41):
FIG. 19 shows a schematic of a PEG-lipid micelle (drawn approximately to scale) . The hydrodynamic radius measured by dynamic light scattering, for micelles made from lipid-PEG.sub.1900 is approximately 85 .ANG. to 100 (Needham, (1992)). If the lipid acyl chains and phospholipid headgroup that comprise the core of the micelle take up 25 .ANG. of the total radius, then the polymer extends approximately 60-75 .ANG. out from this core, which is in close agreement with the polymer extension obtained for the same molecule in bilayers from x-ray diffraction experiments. (Needham, (1992)). These results indicate an extended, "brush-like" conformation for this non-adsorbing, but grafted, polymer.

Detailed Description Text (177):
The geometric characteristics for the micelle and the size of the region occupied by the grafted PEG(750) polymer allow both the MOPC micelle and the region occupied by PEG(750) at the lipid bilayer surface to be drawn to scale (FIG. 10). FIG. 10 shows the relative sizes of the MOPC micelle (spheroid, 66 .ANG..times.86 .ANG.) and the PEG-lipids as "mushrooms" (R.sub.F =19 .ANG.) at the vesicle surface for a surface density equivalent to about 5 mol % PEG-lipid. Knowing these dimensions allows a discussion of how the position of the MOPC micelle at the polymer-grafted interface varies as a function of PEG-lipid concentration, and how this determines the extent to which micelle-membrane fusion can occur, i.e., these geometric features determine the contribution of the excluded area of PEG(750) "mushrooms" to the process of micelle-membrane fusion through an activation energy for fusion.

Detailed Description Text (186):
FIG. 13 provides the theoretical model for the data of FIG. 9, in which the additional work to create a denuded area in a polymer "mushroom"-covered lipid bilayer surface reduces the rate of micelle adsorption. The dependence of uptake on mol % PEG-lipid in the membrane (shown in FIG. 13) is found when the apparent projected area occupied by the micelle in the region of PEG(750) mushrooms is equal to 1400 .ANG..sup.2. This area has a corresponding radius of 21 .ANG., which is slightly less than the maximum radius at the mid plane of the micelle core (33 .ANG.). Such a radius is obtained when a micelle is just touching mushrooms on either side and the headgroups of its lipids penetrate the headgroup region of the membrane lipids by a few Angstroms as shown in FIG. 11A. This result suggests that micelle-membrane fusion requires intimate contact between the micelle and membrane, i.e., transfer of MOPC from micelles to bilayer can only occur if the micelle "physically" touches the lipid surface and even enters the head group region of the bilayer. For a 20 mol % PEG-lipid bilayer, the micelle is completely excluded from the lipid surface, intimate contact cannot be made and micelle-membrane fusion is inhibited, as shown in FIG. 11B.

Detailed Description Text (204):
The concentration at which PEG-lipid (DSPE-PEG2000) forms micellar structures was assessed by a simple fluorescence assay using DPH spectroscopy as described earlier (Example 1), and was found to be approximately 1 micromolar. This second trial used SOPC +20 mol % PEG2000 DSPE (0.2 mg/ml, 2.times.10.sup.-4 M total lipid) for the lipid vesicles and 1 mM PEG2000 DSPE as micellar suspension. Using 0.04 mol % of NED-PC as the dye, bulk fluorescence was observed in the lipid vesicles but the vesicles were very rigid and could not be broken simply with micropipet suction. It was as though the PEG-lipids at this high concentration had formed a gel inside the vesicles. Negative stain electron micrograph pictures (not shown) of PEG-lipid micelles show that they are highly filamentous, suggesting that this gel is some sort of an entangled micellar phase. However, fluorescent micelles of PEG-lipids were shown to be encapsulated inside the giant lipid vesicles and we would expect them to also be encapsulated inside extruded unilamellar vesicles.

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L8: Entry 4 of 12 File: PGPB Aug 7, 2003

DOCUMENT-IDENTIFIER: US 20030147944 A1
TITLE: Lipid carrier compositions with protected surface reactive functions

Summary of Invention Paragraph:
[0006] It has been reported that PEG of about 2000 daltons (Da) is optimal for increasing the circulation time of a liposome while still making the liposome surface available for epitope recognition (Allen, T. A. (1994) Trends in Pharmacological Studies 15(7):215-220). Further, the literature shows that there are limits to the amount of PEG-conjugated lipids that can actually be incorporated into a liposome. This is because the PEG-lipid will form non-bilayer phases such as micelles and non-vesicle structures such as bilayer discs.

Detail Description Paragraph:
[0061] The previous literature suggested that an excess of PEG-lipid will not be incorporated with liposomes, but will form non-bilayer phases such as micelles; Therefore, the incorporation of 15 mol % DSPE-PEG 2000 into 10 mol % PS liposomes was examined with size exclusion chromatography to separate liposomes from DSPE-PEG 2000 micelles. The Bio-Gel A-15 m gel filtration column was first calibrated to resolve the liposomes from DSPE-PEG 2000 micelles by applying liposomes and DSPE-PEG 2000 micelles to the column immediately after mixing. As shown in FIG. 1, no micelle peak was observed in the elution profile of the stock preparation (54 mM) of 10 mol % PS liposomes containing 15 mol % DSPE-PEG 2000. Identical elution profiles were obtained when the stock liposomes were diluted to the concentrations used in in vitro (0.2 mM) and in vivo (6.2 mM) experiments. Based on the ratio of the radiolabeled DSPE-PEG 2000 and liposome marker ([.sup.14C]-CHE), the amount of DSPE-PEG 2000 present in PS liposome containing fractions reflected a DSPE-PEG 2000 composition of 14 mol % for all of the liposome concentrations. This data shows that elevated PEG-lipid content can be incorporated into reactive phospholipids containing liposomes in accordance with this invention, and that alternate lipid phases do not appear to be formed during the preparation or the dilution of such liposomes.

Detail Description Paragraph:
[0070] Liposomes were prepared with 20 mol % PS of varying acyl chain composition. The acyl chain lengths were chosen to be shorter, (C:10) and (C:12), equal (C:14). or longer (C:16) in length to the base lipid, DMPC. 7.5 mol % DPPE-PEG was exchanged from PEG micelles into an aliquot of each of the DMPC/PS liposomes by incubating liposomes and micelles at 37.degree. C. overnight. The PEG was shown to be completely exchanged by size exclusion chromatography on Sepharose C1-4B columns. This results in the outer leaflet having a density of PEG equivalent to a liposome having a total PEG-lipid concentration relative to total lipid content of greater than 10 mol % (equivalent to the liposome having a total PEG-lipid concentration of about 15 mol %). PS liposomes were diluted in tissue culture media (DMEM 10% FBS) and added to LCC6, human breast cancer cells. The cells were incubated with the liposomes overnight, then viability was assessed with a MTT assay. The results are shown in FIG. 5.

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L9: Entry 29 of 29 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885613 A
** See image for Certificate of Correction **
TITLE: Bilayer stabilizing components and their use in forming programmable fusogenic liposomes

Detailed Description Text (24):
Any variety of drugs which are selected to be an appropriate treatment for the disease to be treated in the tissue can be administered using the fusogenic liposomes of the present invention. Often the drug will be an antineoplastic agent, such as vincristine, doxorubicin, cisplatin, bleomycin, cyclophosphamide, methotrexate, streptozotocin, and the like. It may also be desirable to deliver anti-infective agents to specific tissues by the present methods. The compositions of the present invention can also be used for the selective delivery of other drugs including, but not limited to local anesthetics, e.g., dibucaine and chlorpromazine; beta-adrenergic blockers, e.g., propranolol, timolol and labetolol; antihypertensive agents, e.g., clonidine and hydralazine; anti-depressants, e.g., imipramine, amitriptyline and doxepim; anti-convulsants, e.g., phenytoin; antihistamines, e.g., diphenhydramine, chlorphenirimine and promethazine; antibacterial agents, e.g., gentamycin; antifungal agents, e.g., miconazole, terconazole, econazole, isoconazole, butaconazole, clotrimazole, itraconazole, nystatin, naftifine and amphotericin B; antiparasitic agents, hormones, hormone antagonists, immunomodulators, neurotransmitter antagonists, antiglaucoma agents, vitamins, narcotics, and imaging agents. Other particular drugs which can be selectively administered by the compositions of the present invention will be well known to those of skill in the art. Additionally, two or more therapeutic agents may be administered simultaneously if desired, where such agents produce complementary or synergistic effects.

Detailed Description Text (75):
The presence of lipid micelles is not readily apparent from freeze fracture electron microscopy. Lipid in the micellar phase could, however, contribute to the isotropic signal observed in NMR spectra, and it has previously been shown that PEG-PE conjugates form micelles when hydrated in isolation (Woodle and Lasic, Biochim. Biophys. Acta, 113:171-199 (1992)). As such, the presence of micelles was tested by subjecting a suspension of LUVs to molecular sieve chromatography on Sepharose 4B. The liposomes were of the same composition used for the freeze fracture studies above except that DSPE-PEG.sub.2000 was used in place of DOPE-PEG.sub.2000, and they contained trace amounts of .sup.14 C-DPPC and .sup.3 H-DSPE-PEG.sub.2000. The elution profile is shown in FIG. 8. A single peak containing both the phospholipid and PEG-PE conjugate markers was found in the void volume. A control experiment also shown in FIG. 8 demonstrated that micelles, which formed when PEG-PE was hydrated in isolation, were included into the column and would have been clearly resolved if present in the liposomal preparation.

Other Reference Publication (15):
Janoff, A., et al., "Unusual Lipid Structures Selectively Reduce the Toxicity of Amphotericin B," Proc. Natl. Acad. Sci. USA, 85:6122-6126 (1988).

L9: Entry 28 of 29 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6217886 B1
TITLE: Materials and methods for making improved micelle compositions

Brief Summary Text (29):
Of interest to the present invention is work relating to molecular aggregates called "micelles" which are defined as colloidal aggregates spontaneously formed by amphiphilic compounds in water above a critical solute concentration, the critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT). The molecules constituting the micelles are in rapid dynamic equilibrium with the unassociated molecules. The increase in the concentration above the CMC usually leads to an increase in the number of micelles without any change in micellar size; however, in certain cases with phospholipid mixed micelles, the spherical micelles enlarge into rod-shaped micelles (Carey et al., Arch. Inter Med. 130:506-527 (1972); Hjelm, Jr. et al., J. Phys. Chem. 96 (21):8653-8661 (1992)). The CMC is strongly temperature dependent, and at a given concentration the monomer to micelle transition occurs gradually over a broad temperature range (Almgren et al., Colloid Polym. Sci. 273:2-15 (1995)). An increase in the temperature leads to an increase in the number of aggregates, while the hydrodynamic radius remains constant (Nivaggioli et al., Langmuir. 11 (3):730-737 (1995); Alexandridis et al., Langmuir. 11: 1468-1476 (1995)). In general the increase in temperature leads to an increase in hydrophobic interactions and the water dielectric constant is reduced augmenting the ionic repulsion forces. There are many ways to determine the CMC of an amphiphilic compound (surface tension measurements, solubilization of water insoluble dye, or a fluorescent probe, conductivity measurements, light scattering, and the like). According to a preferred method, surface tension measurements may be used to determine the CMC of PEG-DSPE micelles at room temperature.

Brief Summary Text (42):
The present invention provides improved methods of preparing biologically active micelle products comprising one or more biologically active amphipathic compounds in association with a micelle. As used herein, compounds embrace peptides, proteins, enzymes in general, as well as fragments, analogs, and modulators thereof With respect to proteins, the invention contemplates use of both L and D forms. Where compounds of the invention exist in both cis and trans conformations, the invention comprehends use of either form alone or a combination of both forms. The micellar formulations of the invention deliver and enhance bioactivity of the biologically active peptides in a manner which provides improvements in the efficacy and duration of the biological effects of the associated peptides. Increased efficacy and duration of the biological effect is believed to result, at least in part, from interaction of the compound with the micelle in such a manner that the compound attains, and is maintained in, an active or more active conformation than the compound in an aqueous environment. The invention thus overcomes the problems associated with previous liposomal formulations, such as, but not limited to, uptake by the reticuloendothelial system, degradation of the compound, or delivery of the compound in an inactive conformation. According to one aspect of the present invention, polyethylene-glycol (PEG) is covalently conjugated to DSPE and used to form polymeric micelles which are then passively loaded with VIP. The PEG-DSPE forms micelles with a hydrophobic core consisting of distearoyl phosphatidylethanolamine (DSPE) fatty acid chains which is surrounded by a

hydrophilic "shell" formed by the PEG polymer.

Brief Summary Text (44):
As one aspect of the invention, the micelles are sterically stabilized micelles (SSM) which are produced from a combination of lipids which includes at least one lipid component covalently bonded to a water-soluble polymer. This polymer bound phospholipid is the micelle forming component. Other lipids are actually solubilized in this micelle to form mixed micelles. The water-soluble polymer, which is preferably polyethylene glycol (PEG) increases the lipid solubility to form micelles instead of vesicles in aqueous media. It also acts to sterically stabilize the resulting micelle against uptake by components of the reticuloendothelial system.

Brief Summary Text (52):
Methods of the invention for producing sterically stabilized crystalline products are amenable to the use of any compound that is insoluble in an aqueous solution. Preferred insoluble compounds include, but are not limited to, progesterone, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, amphotericin B, betulinic acid, camptothecin, diazepam, nystatin, propofol, cyclosporin A, doxorubicin, and Taxol.RTM.. In methods of the invention for producing sterically stabilized crystalline product further comprising one or more targeting compounds, any targeting compound that assumes or maintains a biologically active conformation when in association with the sterically stabilized crystalline product can be used. In a preferred embodiment, any of the amphipathic compounds as described above are utilized. In a most preferred embodiment, the targeting compound is VIP or other member of the VIP/GRF family or proteins.

Drawing Description Text (2):
FIG. 1 depicts surface tension measurements of a PEG-DSPE aqueous solution to determine the critical micelle concentration (CMC) at room temperature;

Detailed Description Text (3):
In methods of the invention to prepare sterically stabilized crystalline products, any compound that is insoluble in as aqueous solution can be incorporated into to crystalline product. In methods of the invention, the insoluble compounds associate in the hydrophobic core of the associated lipids to the extent that the insoluble compound crystallizes. While the invention contemplates the use of any insoluble compound to produce the crystalline products, preferred compounds are normally insoluble anti-cancer agents, antifungal agents, sedatives, and steroidal compounds. Most preferably, the insoluble compounds are selected from the group consisting of Taxol.RTM., betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, and progesterone.

Detailed Description Text (20):
According to this example, VIP was incorporated into sterically stabilized micelles according to the following procedure. In order to determine the concentration of PEG-DSPE needed to prepare micelles, surface tension studies of PEG-DSPE aqueous solutions were performed. The critical micellar concentration was found to be 0.5 to 1.0 .mu.M, thus 1.0 .mu.M of PEG-DSPE was used to ensure formation of micelles (FIG. 1). PEG-DSPE lipid (1 .mu.mol/ml) was dissolved in chloroform and mixed in a round bottom flask. The organic solvent was evaporated using a rotoevaporater at a bath water temperature of 45.degree. C. (Labconco, Kansas City, Mo.). Complete dryness was achieved by desiccation under vacuum overnight. The dry lipid film was hydrated with saline (0.15 N, pH 6.8) or HEPES buffer (10 mM, pH 7.4). The solution was incubated with human VIP (13 .mu.g/ml) for 30 min before use in circular dichroism. Human VIP (0.1 nmol/ml) was added to the phospholipid micelle suspension and incubated for 2 hours at room temperature before use in cheek pouch studies.

Detailed Description Text (27):

According to the example, CD was used to determine the conformation of VIP in saline, Hepes buffer and phospholipid micelles at room temperature and at 37.degree. C. The CD spectra analysis was performed after 13 .mu.g of human VIP incubated with 1 ml PEG-DSPE (1 .mu.mol) micelles for 30 min at room temperature as determined by preliminary studies. A bandwidth of 1.0 nm and a step resolution of 0.5 nm were used to collect an average of 9 accumulations/sample at near UV range (200-260 nm). The temperature was maintained during spectral analysis by a circulating water bath attached to a jacket surrounding the fused quartz CD cell. The evaluation of VIP molecule conformation in SSM by using circular dichroism was successful because the distortion caused by spherical particles was eliminate due to the small size and univesicular structure of the SSM. The dynamic nature of the micelles also enhanced the VIP interactions with phospholipids. The phospholipid micelles were ideal in our study of VIP conformation since it provided a hydrophobic core similar to the phospholipid bilayer of the SSL. Moreover, both the negative charge, and the hydrophilic layer provided by the PEG mimic the conditions of our SSL and make it possible to infer the VIP conformational results.

Detailed Description Text (64):
According to the present example, micelle composed of two different compositions were prepared and characterized in order to determine an optimal system for increasing solubility of normally water-insoluble compounds. In the first system, micelles were composed of DSPE-PEG and PC. When DSPE-PEG is mixed with phosphatidylcholine (PC) in aqueous medium, mixed micelles are formed instead of liposome bilayers. In the second system, micelles were formed using PC in combination with a representative bile salt, sodium taurocholate (Sigma). When small molecular weight surfactants, such as bile salts, are mixed with DSPE-PEG, formation of spherical mixed micelles can also be detected. The purpose of this study was (i) to compare the effect of DSPE-PEG and bile salts on phosphatidylcholine (PC) capacity to form mixed micelles; (ii) to examine and compare characteristics of the resulting mixed micelles, including micelle-to-vesicle-transition upon dilution; and (iii) to compare solubilization potential of the two micelle systems.

Detailed Description Text (66):
The mean size of the DSPE-PC micelles was consistently larger (17 to 22 nm) than micelles containing bile salts (3 to 5 nm). Aqueous dilutions of bile salt mixed micelles resulted in a detectable micelle-to-vesicle-transition, however, no transition was observed under similar conditions with the DSPE-PEG/PC mixed micelles. Bile salts, when added to preformed PC liposome dispersions, resulted in formation of mixed micelles from the pre-existing liposomes, whereas addition of DSPE-PEG to PC liposomes did not demonstrate any vesicle to micelle transition. These results suggest that the hydrophilic PEG component of the DSPE-PEG molecules prevent micelle/micelle or bilayer/micelle interactions. Since DSPE-PEG did not solubilize liposomes, it is anticipated that it will not solubilize a plasma membrane. This result indicated the potential for lower plasma membrane toxicity of DSPE-PEG than bile salts.

Detailed Description Text (68):
In addition, solubility of progesterone in DSPE-PEG micelles was approximately five to ten times larger than bile salt micelles (from 21 .mu.g/ml to 198.+-.7 .mu.g/ml) for the same total lipid concentration, thereby suggesting that DSPE-PEG micelles have a greater potential as an efficient vehicle for insoluble drugs. However, this dispersion contained both SSM (at approximately 17 nm) and SSC (at approximately 150 nm).

Detailed Description Text (70):
According to the present example, enhanced solubility of normally water-insoluble compounds was further investigated using a DSPE-PEG micelle composition. In addition, a method for preparing micelles comprising a targeting agent in addition to an encapsulated water-insoluble compound was designed. Drug solubility was

determined as follows.

Detailed Description Text (71):
Active drug loading was carried out by adding an excess of drug in powder form to a polyethylene microfuge tube containing PC/bile salt or DSPE-PEG prepared using the film method as previously described in Example 1. Excess drug was removed by centrifugation and the supernatant was analyzed by HPLC. In the case of progesterone, HPLC conditions included a YMC-CN (A-503, 250.times.4.6 mm inner diameter) column, a mobile phase comprising acetonitrile and water (40:60), and a flow rate of 1.5 ml/minute. HPLC eluent was measured with adsorption at 254 nm. For PC/bile salt mixed micelles, the progesterone to lipid ratio was determined to be 0.0156. For DSPE-PEG micelles, the progesterone to lipid ratio was found to be 0.17.

Detailed Description Text (79):
According to this aspect of the invention, the ability of micelle products of the invention to enhance cellular viability following cryopreservation was examined. In this experiment, cells were incubated with either DMSO, DSPE-PEG micelle products, or DSPE-PEG micelles products including VIP for 30 minutes prior to storage for 48 hours in liquid nitrogen. Follow removal from the liquid nitrogen, cells were thawed and viability was measured using Trypan blue using standard techniques.

Other Reference Publication (114):
Zareie, H.M. et al., "STM images of PDLLA-PEG copolymer micelles," Colloids and Surfaces A: Physiochemical and Engineering Aspects, 112:19-24 (1996).

CLAIMS:

31. The method of claim 7, wherein the soluble compound is selected from the group consisting of progesterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, testosterone, betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, and Taxol.RTM..

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L9: Entry 26 of 29 File: USPT Jan 15, 2002

DOCUMENT-IDENTIFIER: US 6338859 B1
TITLE: Polymeric micelle compositions

Brief Summary Text (42):
Additional drugs which can be contained in micelles are conventional hydrophobic antibiotics and antifungal agents such as amphotericin B, poorly water soluble immunomodulators such as cyclosporin, poorly water soluble antiviral drugs such as HIV protease inhibitors and poorly water-soluble steroidal (e.g. dexamethasone), non-steroidal (e.g. indomethacin) anti-inflammatory drugs and genome fragments.

Brief Summary Text (50):
Evidence of drug incorporation can be obtained by GPC or DLS since both methods detect changes in micellar size. The presence of drugs is usually associated with such an increase in the size of micelles. The location of a drug inside the micelle core may be demonstrated by quenching experiments. For instance, iodide (I) which is a water soluble quencher of DOX, does not affect the fluorescence of the micelle-incorporated drug but quenches the fluorescence of the free drug. Such experiments showed that DOX was retained in PEO-PBLA after freeze drying and reconstitution in water. In the case of DOX, the self-association of the drug in the micelle core also results in a decrease in the fluorescence intensity of the drug. Recently, the retention and slow release of amphotericin B from polymeric micelles was indirectly ascertained by measuring the decrease of its hemolytic activity after incorporation into PEO-PBLA micelles.

Brief Summary Paragraph Table (1):
TABLE 1 Examples of drugs and tracers loaded into polymeric micelles Incorporation Micelle size Drug Polymer Mode with drug (nm) Amphotericin B PEO-PBLA P 26 Antisense PEO-P(Lys) EA 50 oligonucleotide Cisplatin PEO-P(Asp) C 16 Cyclophosphamide PEO-P(Lys) C n.a. Dequalinium PEO-PE P 15 Doxirubicin (DOX) PEO-P (Asp) C 50 DOX PEO-P(Asp) C 14-131 DOX PEO-P(Asp) C 17-42 DOX PEO-PBLA P 30 DOX PEO-PDLLA P n.a. DOX PEO-PBLA P 37 DOX PEO-P(Asp) P + C n.a. DOX PNIPA-PBMA P n.a. DOX PAA-PMMA P n.a. Gd-DTPA-PE PEO-PE P 20 .sup.111 In-DTPA-SA Haloperidol PEO-PPO-PEO P n.a. Haloperidol PEO-PPO-PEO P 15 Indomethacin PEO-PBLA P 25-29 Indomethacin PEO-PCL P 145-165 Indomethacin PEO-PCL P 114-156 Iodine derivative PEO-P(Lys) C 80 of benzoic acid KRN-5500 PEO-PBLA P PEO-(C.sub.16, BLA) 71* PEO-P(Asp, BLA) Paclitaxel PEO-PDLLA P n.a. Paclitaxel LCC P <100 Plasmid DNA PEO-P(Lys) EA 140-150 Soybean trypsin PEO-PE P 15 inhibitor Testosterone PEO-PDLLA P n.a. Topoisomerase II PEO-PE P n.a. inhibitor ellipticine n.a.: not available, P: physical entrapment, C: chemical bonding, EA: electrostatic association *After the sonication of PEO (C.sub.16, BLA) aggregates

Detailed Description Text (18):
To investigate drug entrapment efficiency, indomethacin was entrapped in PVP-PDLLA and PEG-PDLLA micelles as shown in Table 4.

Detailed Description Text (20):
The indomethacin entrapment efficiency in PVP-PDLLA and PEG-PDLLA micelles was similar at a low drug level. With increased drug loading, the entrapment efficiency of PVP-PDLLA micelles was superior to that of PEG-PDLLA micelles (considering copolymers having the same molecular weight). Without wishing to be bound by

theory, it is believed that at low drug ratios the drug is first incorporated in the core and then, at higher ratios, it becomes incorporated into the PVP hydrophilic shell.

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L9: Entry 22 of 29 File: USPT May 4, 2004

DOCUMENT-IDENTIFIER: US 6730334 B2
** See image for Certificate of Correction **
TITLE: Multi-arm block copolymers as drug delivery vehicles

Detailed Description Text (187):
The micelle solutions were treated with .about.2.5 ml of 5% SDS solution for 24 hours. The micelle solutions before and after the addition of surfactant (SDS) were characterized after filtration through 0.2 .mu.m syringe filter using a Brookhaven 90 Plus Particle Sizer. Table 4 summarizes the DLS cumulant analysis results. The cumulant diameter of the micelles ranged from 19 to 35 nm before the SDS addition. The DLS measurement was also carried out without filtration, and little alteration of micelle property was seen on the multi-arm block copolymers. BCD-PCL-PEG2.sub.6kDa had the least change in micelle property before and after SDS addition. The other micelles presented dramatic change in size and significant decrease in count rate. The count rate of the BCD-PCL-PEG2.sub.6kDa micelles was reduced by 30%. This was likely due to the dilution of the micelle solution rather than the dissociation of micelles. Multi-armed PEG block copolymers with higher number of arms tend to be less aggregated.

Detailed Description Paragraph Table (8):
TABLE 8 DLS cumulant analysis results of BCD-PCL-(PEG3k).sub.2, 8-arm-PCL-PEG2.sub.6kDa, and linear PEG-PCL micelles Concentration Count rate % Count Samples (mg/mL) Diameter (nm) Dispersity (keps) Remaining BCD-PCL-PEG2.sub.6kDa 2 3.34 19.8 0.098 52.7 Before filter BCD-PCL-PEG2.sub.6kDa 3.34 19.4 0.058 44.2 After filter BCD-PCL-PEG2.sub.6kDa + 3.34 22.7 0.152 30.7 69.45701357 SDS 8-arm-PCL-PEG2.sub.6kDa 3.24 Before filter 8-arm-PCL-PEG2.sub.6kDa 3.24 26.8 0.158 107.1 After filter 8-arm-PCL-PEG2.sub.6kDa + 3.24 42.2 0.24 23.5 21.94211018 SDS Linear PEG-PCL 2.88 Before filter Linear PEG-PCL 2.88 35.6 0.006 348.7 After filter Linear PEG-PCL + SDS 2.88 11 0.401 11 3.154574132

Other Reference Publication (12):
Piskin et al., "Novel PDLLA/PEG copolymer micelles as drug carriers", J. Biomater. Sci. Polymer Edn, 1995, pp. 359-373, vol. 7, No. 4.

Other Reference Publication (17):
Yu et al., "Polymeric micelles for drug delivery: solubiliazation and haemolytic activity of amphotericin B", Journal of Controlled Release, 1998, pp. 131-136, vol. 53.

L9: Entry 21 of 29 File: USPT Dec 28, 2004

DOCUMENT-IDENTIFIER: US 6835718 B2
TITLE: Biocleavable micelle compositions for use as drug carriers

Detailed Description Text (9):
various antibiotics including derivatives and analogs such as penicillin derivatives (i.e. ampicillin), anthracyclines (i.e. doxorubicin, daunorubicin, mitoxantrone), butoconazole, camptothecin, chalcomycin, chartreusin, chrysomicins (V and M), chloramphenicol, chlorotetracyclines, clomocyclines, cyclosporins, ellipticines, filipins, fungichromins, griseofulvin, griseoviridin, guamecyclines, macrolides (i.e. amphotericins, chlorothricin), methicillins, nystatins, chrymutasins, elsamicin, gilvocarin, ravidomycin, lankacidin-group antibiotics (i.e. lankamycin), mitomycin, teramycins, tetracyclines, wortmannins;

Detailed Description Text (106):
Examples of suitable substances for use in amphiphilic molecules are certain proteins, polypeptides, polyamino acids, glycoproteins, lipoproteins (i.e. low density lipoprotein), nucleic acid polymers, DNA, RNA, amino sugars, glucosamines, polysaccharides, lipopolysaccharides, amino polysaccharides, polyglutamic acids, poly lactic acids (PLA), polylysines, polyethylenimines, polyacrylamides, nylons, poly(allylamines), lipids, glycolipids and suitable synthetic polymers, especially biopolymers, resins and surfactants, as well as suitable derivatives of these substances. Also included as suitable substances are the polymers disclosed in U.S. Pat. No. 4,645,646. Also preferred for use in amphiphilic molecules are N-(2-hydroxypropyl) methacrylamide (HPMA), HPMA derivatives, poly cyanoacrylates such as poly(butyl cyanoacrylate), poly(isobutyl or isohexyl cyanoacrylate), polyethylene glycol (PEG), any micelle-forming PEG derivatives, poly (D,L-lactic-coglycolic acid) (PLGA), PLGA derivatives and poly (D,L-lactide)-block-methoxypolyethylene glycol (diblock).

Detailed Description Text (174):
A Biocleavable Surfactant Crosslinked to Entrap Amphotericin

Detailed Description Text (175):
In this example hydrazine-linked Tween 20 is thiolated and used to entrap amphotericin B in micelles. The micelles are then crosslinked through the thiol groups to form a polymer.

Detailed Description Text (177):
For preparation of amphotericin-loaded micelles, about 45 mg of thiolated surfactant was dissolved in about 0.3 ml of 50% dimethylformamide (DMF) in 0.0125 M potassium phosphate buffered water, pH 6.5. Then about 0.76 mg of citraconic anhydride-treated amphotericin B in 0.05 ml of DMF was added and mixed, resulting in a yellow suspension. The final volume was adjusted to 0.5 ml with 50% DMF.

Detailed Description Text (178):
For crosslinking, about 1.8 mg of 1,1'(methylenedi-4,1-phenylene) bismaleimide IPBM) dissolved in 0.025 ml DMF was added, mixed and left overnight. A yellow, polymerized precipitate was separated by centrifugation and the supernatant removed. The precipitate was further crosslinked with 1.4 mg of MPBM in 0.020 ml DMF for 2 hours. The precipitate was then washed 3 times by mixing and soaking it

in 1 ml of 50% DMF, centrifuging and removing the supernatant. After the third wash, the precipitate was still very yellow due to amphotericin while the supernatant was only slightly yellow and clear. This showed that the crosslinked surfactant had entrapped a significant amount of amphotericin that was not readily extracted.

CLAIMS:

3. The composition of claim 1 wherein the active agent is selected from the group consisting of amphotericins, camptothecins, ganciclovir, furosemide, indometbacin, chiorpromazine, methotrexate, penicillins, anthracyclines, teramycins, tetracyclines, chiorotetracyclines, clomocyclines, cyclosporins, butoconazole, charteusin, elsamicin, ellipticines, guamecyclines, macrolides, filipins, fungichromins, nystatins, 5'-fluorouracil, 5'-fluoro-2'-deoxyuridine, allopurinol, taxanes and wortmannin.

10. The composition of claim 8 wherein the active agent is selected from the group consisting of amphotericins, camptothecins, ganciclovir, furosemide, indomethacin, chiorpromazine, methotrexate, penicillins, anthracyclines, teramycins, tetracyclines, chlorotetracyclines, clomocyclines, cyclosporins, butoconazole, charteusin, elsamicin, ellipticines, guamecyclines, macrolides, filipins, fungichromins, nystatins, 5'-fluorouracil, 5'-fluoro-2'-deoxyuridine, allopurinol, taxanes and wortmannin.

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L12: Entry 8 of 8 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885613 A
** See image for Certificate of Correction **
TITLE: Bilayer stabilizing components and their use in forming programmable fusogenic liposomes

Detailed Description Text (24):
Any variety of drugs which are selected to be an appropriate treatment for the disease to be treated in the tissue can be administered using the fusogenic liposomes of the present invention. Often the drug will be an antineoplastic agent, such as vincristine, doxorubicin, cisplatin, bleomycin, cyclophosphamide, methotrexate, streptozotocin, and the like. It may also be desirable to deliver anti-infective agents to specific tissues by the present methods. The compositions of the present invention can also be used for the selective delivery of other drugs including, but not limited to local anesthetics, e.g., dibucaine and chlorpromazine; beta-adrenergic blockers, e.g., propranolol, timolol and labetolol; antihypertensive agents, e.g., clonidine and hydralazine; anti-depressants, e.g., imipramine, amitriptyline and doxepim; anti-convulsants, e.g., phenytoin; antihistamines, e.g., diphenhydramine, chlorpheniramine and promethazine; antibacterial agents, e.g., gentamycin; antifungal agents, e.g., miconazole, terconazole, econazole, isoconazole, butaconazole, clotrimazole, itraconazole, nystatin, naftifine and amphotericin B; antiparasitic agents, hormones, hormone antagonists, immunomodulators, neurotransmitter antagonists, antiglaucoma agents, vitamins, narcotics, and imaging agents. Other particular drugs which can be selectively administered by the compositions of the present invention will be well known to those of skill in the art. Additionally, two or more therapeutic agents may be administered simultaneously if desired, where such agents produce complementary or synergistic effects.

Detailed Description Text (75):
The presence of lipid micelles is not readily apparent from freeze fracture electron microscopy. Lipid in the micellar phase could, however, contribute to the isotropic signal observed in NMR spectra, and it has previously been shown that PEG-PE conjugates form micelles when hydrated in isolation (Woodle and Lasic, Biochim. Biophys. Acta, 113:171-199 (1992)). As such, the presence of micelles was tested by subjecting a suspension of LUVs to molecular sieve chromatography on Sepharose 4B. The liposomes were of the same composition used for the freeze fracture studies above except that DSPE-PEG.sub.2000 was used in place of DOPE-PEG.sub.2000, and they contained trace amounts of .sup.14 C-DPPC and .sup.3 H-DSPE-PEG.sub.2000. The elution profile is shown in FIG. 8. A single peak containing both the phospholipid and PEG-PE conjugate markers was found in the void volume. A control experiment also shown in FIG. 8 demonstrated that micelles, which formed when PEG-PE was hydrated in isolation, were included into the column and would have been clearly resolved if present in the liposomal preparation.

Other Reference Publication (15):
Janoff, A., et al., "Unusual Lipid Structures Selectively Reduce the Toxicity of Amphotericin B," Proc. Natl. Acad. Sci. USA, 85:6122-6126 (1988).

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L12: Entry 7 of 8 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6217886 B1
TITLE: Materials and methods for making improved micelle compositions

Brief Summary Text (29):
Of interest to the present invention is work relating to molecular aggregates called "micelles" which are defined as colloidal aggregates spontaneously formed by amphiphilic compounds in water above a critical solute concentration, the critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT). The molecules constituting the micelles are in rapid dynamic equilibrium with the unassociated molecules. The increase in the concentration above the CMC usually leads to an increase in the number of micelles without any change in micellar size; however, in certain cases with phospholipid mixed micelles, the spherical micelles enlarge into rod-shaped micelles (Carey et al., Arch. Inter Med. 130:506-527 (1972); Hjelm, Jr. et al., J. Phys. Chem. 96 (21):8653-8661 (1992)). The CMC is strongly temperature dependent, and at a given concentration the monomer to micelle transition occurs gradually over a broad temperature range (Almgren et al., Colloid Polym. Sci. 273:2-15 (1995)). An increase in the temperature leads to an increase in the number of aggregates, while the hydrodynamic radius remains constant (Nivaggioli et al., Langmuir. 11 (3):730-737 (1995); Alexandridis et al., Langmuir. 11: 1468-1476 (1995)). In general the increase in temperature leads to an increase in hydrophobic interactions and the water dielectric constant is reduced augmenting the ionic repulsion forces. There are many ways to determine the CMC of an amphiphilic compound (surface tension measurements, solubilization of water insoluble dye, or a fluorescent probe, conductivity measurements, light scattering, and the like). According to a preferred method, surface tension measurements may be used to determine the CMC of PEG-DSPE micelles at room temperature.

Brief Summary Text (42):
The present invention provides improved methods of preparing biologically active micelle products comprising one or more biologically active amphipathic compounds in association with a micelle. As used herein, compounds embrace peptides, proteins, enzymes in general, as well as fragments, analogs, and modulators thereof With respect to proteins, the invention contemplates use of both L and D forms. Where compounds of the invention exist in both cis and trans conformations, the invention comprehends use of either form alone or a combination of both forms. The micellar formulations of the invention deliver and enhance bioactivity of the biologically active peptides in a manner which provides improvements in the efficacy and duration of the biological effects of the associated peptides. Increased efficacy and duration of the biological effect is believed to result, at least in part, from interaction of the compound with the micelle in such a manner that the compound attains, and is maintained in, an active or more active conformation than the compound in an aqueous environment. The invention thus overcomes the problems associated with previous liposomal formulations, such as, but not limited to, uptake by the reticuloendothelial system, degradation of the compound, or delivery of the compound in an inactive conformation. According to one aspect of the present invention, polyethylene-glycol (PEG) is covalently conjugated to DSPE and used to form polymeric micelles which are then passively loaded with VIP. The PEG-DSPE forms micelles with a hydrophobic core consisting of distearoyl phosphatidylethanolamine (DSPE) fatty acid chains which is surrounded by a

hydrophilic "shell" formed by the PEG polymer.

Brief Summary Text (52):
Methods of the invention for producing sterically stabilized crystalline products are amenable to the use of any compound that is insoluble in an aqueous solution. Preferred insoluble compounds include, but are not limited to, progesterone, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, amphotericin B, betulinic acid, camptothecin, diazepam, nystatin, propofol, cyclosporin A, doxorubicin, and Taxol.RTM.. In methods of the invention for producing sterically stabilized crystalline product further comprising one or more targeting compounds, any targeting compound that assumes or maintains a biologically active conformation when in association with the sterically stabilized crystalline product can be used. In a preferred embodiment, any of the amphipathic compounds as described above are utilized. In a most preferred embodiment, the targeting compound is VIP or other member of the VIP/GRF family or proteins.

Drawing Description Text (2):
FIG. 1 depicts surface tension measurements of a PEG-DSPE aqueous solution to determine the critical micelle concentration (CMC) at room temperature;

Detailed Description Text (3):
In methods of the invention to prepare sterically stabilized crystalline products, any compound that is insoluble in as aqueous solution can be incorporated into to crystalline product. In methods of the invention, the insoluble compounds associate in the hydrophobic core of the associated lipids to the extent that the insoluble compound crystallizes. While the invention contemplates the use of any insoluble compound to produce the crystalline products, preferred compounds are normally insoluble anti-cancer agents, antifungal agents, sedatives, and steroidal compounds. Most preferably, the insoluble compounds are selected from the group consisting of Taxol.RTM., betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, and progesterone.

Detailed Description Text (20):
According to this example, VIP was incorporated into sterically stabilized micelles according to the following procedure. In order to determine the concentration of PEG-DSPE needed to prepare micelles, surface tension studies of PEG-DSPE aqueous solutions were performed. The critical micellar concentration was found to be 0.5 to 1.0 .mu.M, thus 1.0 .mu.M of PEG-DSPE was used to ensure formation of micelles (FIG. 1). PEG-DSPE lipid (1 .mu.mol/ml) was dissolved in chloroform and mixed in a round bottom flask. The organic solvent was evaporated using a rotoevaporater at a bath water temperature of 45.degree. C. (Labconco, Kansas City, Mo.). Complete dryness was achieved by desiccation under vacuum overnight. The dry lipid film was hydrated with saline (0.15 N, pH 6.8) or HEPES buffer (10 mM, pH 7.4). The solution was incubated with human VIP (13 .mu.g/ml) for 30 min before use in circular dichroism. Human VIP (0.1 nmol/ml) was added to the phospholipid micelle suspension and incubated for 2 hours at room temperature before use in cheek pouch studies.

Detailed Description Text (27):
According to the example, CD was used to determine the conformation of VIP in saline, Hepes buffer and phospholipid micelles at room temperature and at 37.degree. C. The CD spectra analysis was performed after 13 .mu.g of human VIP incubated with 1 ml PEG-DSPE (1 .mu.mol) micelles for 30 min at room temperature as determined by preliminary studies. A bandwidth of 1.0 nm and a step resolution of 0.5 nm were used to collect an average of 9 accumulations/sample at near UV range (200-260 nm). The temperature was maintained during spectral analysis by a circulating water bath attached to a jacket surrounding the fused quartz CD cell. The evaluation of VIP molecule conformation in SSM by using circular dichroism was successful because the distortion caused by spherical particles was eliminate due to the small size and univesicular structure of the SSM. The dynamic nature of the

micelles also enhanced the VIP interactions with phospholipids. The phospholipid micelles were ideal in our study of VIP conformation since it provided a hydrophobic core similar to the phospholipid bilayer of the SSL. Moreover, both the negative charge, and the hydrophilic layer provided by the PEG mimic the conditions of our SSL and make it possible to infer the VIP conformational results.

CLAIMS:

31. The method of claim 7, wherein the soluble compound is selected from the group consisting of progesterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, testosterone, betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, and Taxol.RTM..

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